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## Identifying patients who can improve fertility with myomectomy



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#### ABSTRACT

*Objective*: To identify the characteristics of cases and fibroids that will indicate which patients should undergo myomectomy to improve fertility.

Materials and methods: We recruited patients (n = 101) who had undergone myomectomy to improve fertility and received follow-up care for at least six months by the hospital. Medical records were retrospectively reviewed to analyze the pregnancy rates after myomectomy and to identify clinical factors that correlate with pregnancy rates. Cumulative pregnancy rates were analyzed using the Kaplan–Meier method and the Log rank test. The patients were then divided into three groups according to the timing of the myomectomy. The analysis was performed for all patients, for patients in the post-superovulation and/or intrauterine insemination (post-SO/IUI) group and the post-assisted reproductive technology (post-ART) group combined, and for patients in the post-ART group.

Results: Sixty-three pregnancies were achieved by 58 patients (57.4%) who underwent myomectomy. The mean time period between surgery and conception was 9.8 months. Most pregnancies (91.5%) were achieved within two years after surgery. Pregnancy rates were higher in patients aged less than 36 years, with no male factors, and without severe endometriosis, in comparison with patients 36 years of age or older (p < 0.05), with male factor (p < 0.05), and severe endometriosis (p < 0.05). In the analysis of the post-ART group, pregnancy rates were higher (p < 0.05) in cases where enucleation had penetrated the endometrial cavity in comparison with patients where the cavity was not penetrated; however, fibroid characteristics did not correlate with the post-myomectomy pregnancy rate in the post-SO/IUI plus post-ART group.

Conclusion: Post-myomectomy pregnancy rates were higher in women who did not have additional infertility factors. These results suggest that the removal of fibroids benefits especially patients who suffer from infertility of an otherwise unknown cause: surgery should be strongly recommended for these patients. Our study also shows the difficulty in identifying fibroids for removal to improve fertility. Further studies are needed to develop new diagnostic techniques for identifying patients who can improve fertility with myomectomy.

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#### Introduction

Uterine fibroids are known to cause infertility [1]. Clinical evidence suggests that, in decreasing order of importance, submucous, intramural and subserosal fibroids cause infertility [2]. The number of fibroids and the dimension of the lesion appear to affect fertility [2–4].

Although many studies demonstrate that fibroids reduce fertility, only one study demonstrates better pregnancy rates after myomectomy [5]. A recent comprehensive review concluded that

the benefits of myomectomy had not been demonstrated consistently, by stating: 'myomectomy for submucosal fibroids greater than 2 cm and for fibroids distorting the endometrial contour likely confers improvement of fertility outcome' [6]. However, this was not supported by any solid evidence that clarified the type of fibroids and associated benefit of removal. Moreover, studies to identify factors that could impact on the benefits of myomectomy, such as age, male factor, tubal factor and endometriosis, have not been attempted. As a consequence, guidelines for the management of fibroids in infertility cases are not currently available.

The aim of this study was to identify the characteristics of 'cases' and 'fibroids' that should undergo myomectomy to improve fertility. We therefore conducted a retrospective study with 101

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infertility patients who had undergone myomectomy according to the hospital's management protocol.

#### Materials and methods

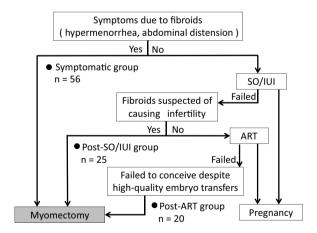
The study protocol was approved by the Institutional Review Board of the University of Tokyo. All procedures were in accordance with the WMA Declaration of Helsinki.

#### **Patients**

The medical records of 805 women who underwent myomectomy at the University of Tokyo Hospital between January 2001 and December 2010 were retrospectively analyzed. A total of 101 patients who underwent myomectomy for the purpose of improving fertility and who had received at least six months' follow-up care were included in this study. The mean follow-up period was 19 (6-103) months. Myomectomy methods were either laparoscopic (n = 55), laparoscopically assisted with small laparotomy (n = 36) or abdominal (n = 10).

Protocol for the management of fibroid with infertility

Fig. 1 indicates our protocol for the management of fibroid with infertility. Myomectomy is planned for patients who have symptoms such as hypermenorrhea and abdominal distention, due to submucous fibroids or extremely large fibroids (symptomatic group). For patients who present with no other symptoms, fibroids are managed expectantly and superovulations and/or intrauterine inseminations (SO/IUI) are commenced. After SO/IUI, approximately 40% of patients achieve pregnancy. When pregnancy has not been achieved after 3–4 attempts of SO/IUI, the impact of fibroids on the anatomy of the endometrial cavity is evaluated by ultrasound, magnetic resonance imaging (MRI) and hysteroscopy. When fibroids are suspected of affecting fertility, as can be the case when fibroids deform the endometrial cavity, myomectomy is



**Fig. 1.** Protocol for the management of fibroids (with infertility) in our hospital. For patients who have symptoms (symptomatic group) (e.g. hypermenorrhea and abdominal distention due to fibroids or extremely large fibroids), myomectomy is planned. For patients who do not present with symptoms, fibroids are managed expectantly and superovulation and/or intrauterine insemination (SO/IUI) are initiated. When pregnancy is not achieved after 3–4 attempts of SO/IUI, the impact of fibroids on infertility is evaluated by ultrasound, MRI and hysteroscopy. When we suspect that fertility is affected by deformation of the endometrial cavity, myomectomy is planned (post-SO/IUI group). In contrast, assisted reproductive technology (ART) is recommended for patients with fibroids that are not known to affect fertility, such as subserosal fibroids. If pregnancy is not achieved despite repetitive high quality embryo transfers, myomectomy is performed (post-ART group). Groupings were as follows: symptomatic group (n = 56); post-SO/IUI group (n = 25), and post-ART group (n = 20).

planned (post-SO/IUI group). In contrast, assisted reproductive technology (ART) is recommended for patients who have fibroids (e.g. subserosal) that do not appear to affect fertility. If pregnancy is not achieved despite repetitive high quality embryo transfers, myomectomy is performed (post-ART group). According to this protocol, approximately one-fourth of patients harboring fibroids but not having symptoms eventually undergo myomectomy. SO/IUI or ART is repeated 3–6 months after myomectomy. Of the 101 patients in the study, patients were allocated as follows: symptomatic group (n = 56); post-SO/IUI group (n = 25); and post-ART group (n = 20).

#### Data analysis

The following factors were analyzed to determine correlations with pregnancy rates after myomectomy: age in years, presence of male factor, tubal factor, severe endometriosis, deformity of the uterine cavity due to fibroids, penetration of the endometrial cavity during enucleation, intramural fibroids, number of enucleated fibroids, total weight of enucleated fibroids and diameter of the largest fibroid.

Male factor was defined as less than 10,000,000 ml<sup>-1</sup> of total zoospermia in the semen sample from the partner. Tubal factor was defined as either obstruction or peritubal adhesion in one or both fallopian tube(s) evaluated by either pre-operative hysterosalpingography or tubal chromotubation during surgery. Stage IV endometriosis (revised American Society for Reproductive Medicine score) was deemed severe endometriosis All patients underwent MRI in 1–2 months before surgery, and one observer (TS) analyzed deformity of the uterine cavity due to fibroids.

Pregnancy was defined as the presence of gestational sac, detected in the uterus by ultrasonography. Cumulative pregnancy rates after myomectomy were analyzed using the Kaplan–Meier method and the log rank test. The analysis was performed for all patients, for patients in the post-SO/IUI and post-ART group combined, and the post-ART group.

#### Results

During the observation period after myomectomy, 63 pregnancies were achieved in 58 patients (57.4%). Of the 63 pregnancies, 24 (38.1%) were conceived spontaneously, 11 (17.5%) were conceived after non-ART treatments and 28 (44.4%) were conceived after ART. The mean time period between surgery and conception was 9.8 months. Most pregnancies (91.5%) were achieved within two years after surgery.

Younger patients (<36 years) without male factor and severe endometriosis had significantly higher pregnancy rates in comparison with older patients ( $\ge$ 36 years, p < 0.05) with male factor (p < 0.05) and severe endometriosis (p < 0.05) (Fig. 2). Tubal factor did not affect the pregnancy rate. Patients with any infertility factor ( $\ge$ 36 years, male factor, tubal factor and severe endometriosis) had a marginally lower pregnancy rate (p = 0.0505) in comparison with women without infertility factors, although the difference did not reach statistical significance.

Deformity of the uterine cavity, penetration of the endometrial cavity, intramural fibroids, number of enucleated fibroids and total weight of fibroids did not affect the pregnancy rate, but the analysis of fibroid size indicated that patients with smaller fibroids ( $\leq 4$  cm in diameter) had a significantly higher pregnancy rate (p < 0.05) than patients with larger fibroids (Fig. 3).

In order to eliminate inherent background bias, we excluded the symptomatic group and re-analyzed cumulative pregnancy rates after myomectomy for patients in the post-SO/IUI and post-ART group. Independent analysis indicated that deformity of the uterine cavity, penetration of the endometrial cavity and location

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